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## The Recognition of HPV Infection as a Risk Factor for Cardiovascular Disease in Men

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## **Abstract**

Human papilloma virus (HPV) is the most common sexually transmitted infection. Strains 16 and 18 are causes of cervical, anogenital, and oropharyngeal cancer. A study found a nearly 3-fold increase in incidence of cardiovascular (CV) events, i.e. stroke and myocardial infarction (MI), in HPV-infected women. HPV-16 and 18 contain protein E6 that binds to p53 tumor suppressor protein, which aids in regulating atherosclerosis, and causes p53 protein degeneration. Additional studies have linked absence of p53 protein to accumulation of atherosclerosis in the body, which is the leading cause of CV events. Presented is a case of a 55-year old male who was found to have HPV16+ tonsillar cancer that suffered from an MI. HPV infection may have been a compounding risk factor for the development of this patient's atherosclerosis. Based on the available research, it is plausible that HPV infection is a risk factor for cardiovascular disease in men.

## **Introduction**

Human papilloma virus (HPV) is the most common sexually transmitted infection in the United States. Oncogenic strains, such as 16 and 18, have been implicated in causing cervical, penile, anal, and oropharyngeal cancers. Oncogenic strains have been shown to be associated with nearly a three-fold increase in cardiovascular (CV) events among infected women.<sup>1</sup> Research thus far has focused on the link between HPV infection and CV events in women exclusively. However, we present a case of a 55-year old male with HPV16+ oropharyngeal cancer who suffered from a myocardial infarction (MI) secondary to coronary artery disease (CAD) with minimal preexisting risk factors. The pathophysiology of HPV-induced deletion of tumor suppressor genes and their contribution to atherosclerosis will be discussed. The probable significance of these deletions and the research performed thus far will also be discussed.

## **Case Synopsis**

A 55-year old white male with a history of gastroesophageal reflux, mild hyperlipidemia controlled on 20 mg of Pravastatin, hypertension controlled on 240 mg of verapamil, and a 50 pack year smoking history presented to our family practice office complaining of retrosternal chest pain without radiation for one week, four episodes of non-bilious, non-bloody vomiting, and one episode of hemoptysis with minimal blood. He originally attributed his chest pain to reflux, but came to the office when it was not relieved with 40 mg of Nexium. He denied dyspnea on exertion, palpitations, shortness of breath, chills, edema, melena, hematemesis, abdominal pain, and chronic cough. The patient had no previous history of CAD or other comorbid conditions.

Upon physical examination, he was found to have a +4 left tonsil that was erythematous and exudative. The right tonsil was without any abnormalities. The patient also had enlarged, fixed lymph nodes in the area of the left submandibular and anterior cervical chains without any supraclavicular lymph nodes. There was no right-sided lymphadenopathy. Cardiovascular, respiratory, and abdominal examinations were without any abnormalities. Due to financial reasons, the patient denied having an EKG performed in the office and was therefore advised to immediately go to the emergency department (ED) for treatment of a suspected MI and left tonsillar cancer. While inpatient at the hospital, the patient was

found to have a complete occlusion of the left circumflex artery, 30% occlusion of the right coronary artery, and 20% occlusion of the left anterior descending artery. He suffered from a non-ST elevation MI.

He had a cardiac stent placed in his left circumflex artery without complications. This relieved his cardiac symptoms. Additionally, a CT scan of his head and neck revealed an enlarged left tonsil that was 2.5X2.2 cm with a 7 mm nodule in the left upper lobe with ipsilateral level 2 and 3 lymphadenopathy. He was diagnosed with Stage 4a squamous cell cancer of the left tonsil that was HPV16+. The patient completed three rounds of cisplatin 40 mg/m<sup>2</sup> and 72 gray of radiation in 36 fractions over 71 days for his oropharyngeal cancer and currently remains in remission. The patient suffers from no residual effects from the MI or oropharyngeal cancer. Despite having some risk factors for cardiovascular disease (CVD), HPV infection may have been associated in causing his MI at an early age and causing such severe atherosclerosis.

### **Literature Review**

While it is well known that oncogenic strains of HPV can cause oropharyngeal, cervical, penile, and anal cancer, research conducted currently suggests that HPV infection leads to an increase in CV events in women. A study found that there is a 2.46X increase in CV events among women infected with HPV infection, regardless of strain, compared to women without HPV infection. The study then took into account whether infection was with oncogenic strains of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68) and found a further increase risk of CV events. Women infected with oncogenic strains of HPV had a 2.86X increase in CV events than women without any HPV infection. The study accounted for preexisting CV risk factors such as diabetes, smoking, hypertension, demographic differences, and health behaviors and found no significant change in results, proving that HPV is an independent risk factor for CV events in women.<sup>1</sup> This study showed that, overall, HPV infection increases risk of CV events in women, but CV event risk further increases in women with infection of oncogenic strains of HPV.

This study is supported by the pathophysiology of HPV and the likely role it plays in the control of atherosclerosis. HPV16 and 18, contain protein E6 that binds specifically to tumor suppressor p53 protein, an important protector of the molecular genome, and causes a cascade of events that lead to

tumor suppressor protein p53's degradation through the ubiquitin pathway.<sup>2</sup> Tumor suppressor protein p53 gene is crucial in the regulation of atherosclerosis. Absence of p53 has been shown to increase atherosclerosis, increase plaque formation in arteries, and decrease apoptosis of infected cells in vivo and in human studies.<sup>1,2,3</sup> Thus, since HPV causes this protein's destruction, atherosclerosis in the human body increases, and this is the proposed mechanism of how HPV increases risk and incidence of cardiovascular events.

Another study evaluated biopsies of atheromatous coronary arteries of 20 males and females who died of MIs and found that 55% of the arteries contained positive polymerase chain reactions (PCRs) for HPV. Nine of the eleven samples were HPV16 and 18 gene sequences. Three samples were both 16 and 18 positive, and two of these patients had MIs before age 35 years of age. This could be of great significance as this suggests that because of their double positive oncogenic HPV status, it lead to premature atherosclerotic disease and early CV events. Past medical history of these patients remains unknown, but it is highly likely that HPV status played a large role in their MIs. This study further suggests the probable role HPV plays in atherosclerotic plaque formation.<sup>3</sup> This study also showed that primarily oncogenic strains of HPV were found in the plaques.

Zfp148 is a protein that naturally suppresses the activity of p53 tumor suppressor genes. Mice with an induced Zfp148 deletion showed increased p53 activity and, compared to mice without the deletion, had smaller plaque formation in the aorta.<sup>4</sup> This is another example of the positive effect p53 has on atheromas and how deletion of such gene could cause an increase in atheromatous plaque formation.

### **Case Conceptualization**

While infection with oncogenic HPV strains like 16 and 18 have proven to increase CV events in women by almost 3 times by increasing atherosclerosis, there is no evidence or ongoing research to prove the same in men. There are many studies that support the hypothesis that the pathophysiology of HPV and it's ability to degrade tumor suppressor p53 lead to increased atherosclerosis. This pathophysiology was proven in mice and in studies that were not gender specific. However, the lack of information or even research being conducted to prove the connection between HPV and CV risk in men is non-existent. This

is unfortunate because heart disease secondary to atherosclerosis is the leading cause of premature death and disability in developed countries in both men and women. Atherosclerosis can not only lead to MIs and strokes, but also angina pectoris, transient ischemic attacks, intermittent claudication, and mesenteric ischemia, depending on where plaques form in the vasculature.<sup>5</sup> Since HPV research, data, and vaccination guidelines have historically been years behind in men, research must be conducted to define this risk. The acceptance rate for most immunizations ranges from 80-90%, especially for more well-established vaccines. However, the acceptance rate is much lower for HPV vaccine, with 57.3% of females and 34.6% of males initiating the series and only 38% of females and 14% of males receiving all three doses.<sup>6,7</sup>

This case is unique in that the patient is a male, who had many similarities with the research that was performed in women. The patient had HPV16+ oropharyngeal cancer, indicating infection with an oncogenic strain of HPV, and suffered from an MI that was due to 100% occlusion of the left circumflex. In addition, he had partial occlusions of the right coronary artery and left anterior descending. The left anterior descending artery has a common predilection for atherosclerotic plaques.<sup>5</sup> The patient did have some preexisting risk factors for his MI, including his 50 pack year smoking history, hypertension, and mild hyperlipidemia; however, it cannot be ruled out that this CV event was secondary to HPV16+ infection or that HPV infection was a contributing factor that led to such severe atherosclerosis. His calculated 10-year CV risk at the time of the MI was only 24.8%. This was calculated using his age, gender, race, non-diabetic status, smoking status, total cholesterol, HDL, systolic blood pressure, and use of blood pressure medication. Based on this calculated risk, he was appropriately being treated with a moderate intensity statin.

According to the study performed by Hsu-Ko and Fujise, after controlling for preexisting conditions that put patients at risk for stroke or MI like smoking, diabetes, hypertension, demographics, and differences in health behaviors, HPV-infection is an independent risk factor for increased CV event incidence among women.<sup>1</sup> It is possible then that HPV16+ infection, which had been manifesting for an unknown amount of time in this male patient could have been a contributing factor to his MI and severe

atherosclerosis. The patient has not experienced any additional CV events since the NSTEMI, but continues to take 20 mg of Pravastatin for his cholesterol/lipid management.

Unfortunately, only one conclusive study has been performed in women to show the connection between HPV-16 and 18 infection and increased cardiovascular risk. The results that were published are promising, and a link seems to be very likely. Since no research has been performed in men with HPV infection, it is not possible to conclusively define HPV infection as an independent or even concomitant risk factor for increased CVD and CV events, but this case study in combination with the existing literature points to a strong relationship between the two.

## **Conclusion**

Recent studies have documented that HPV is a compounding risk factor for CV events in women, but no such studies were performed in men. However, based off of this case study of a 55-year old male with HPV16 + tonsillar cancer who suffered from an MI, and the ability of HPV16 and 18's to deregulate tumor suppressor genes that control atherosclerosis, HPV infection with oncogenic strains could be a risk factor for CV events in both genders. In the case of this patient, his HPV16+ status could have been an additional factor in causing his MI. More research must be performed in order for this risk to be documented. Then, aggressive preventative action can be taken in individuals with documented HPV infection with oncogenic strains, HPV vaccination guidelines may be adjusted or extended, and efforts can be taken to increase public awareness and vaccination compliance, especially among males.



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